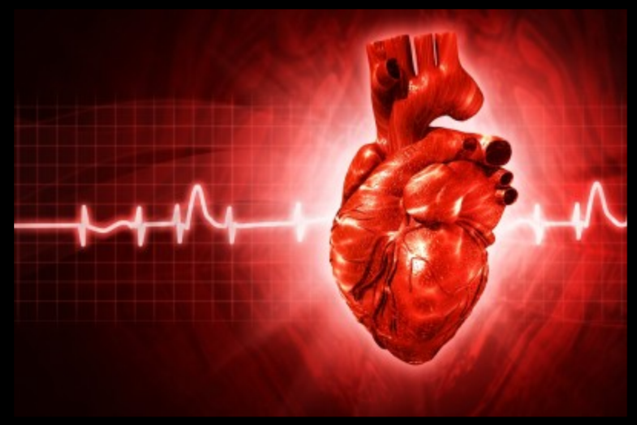
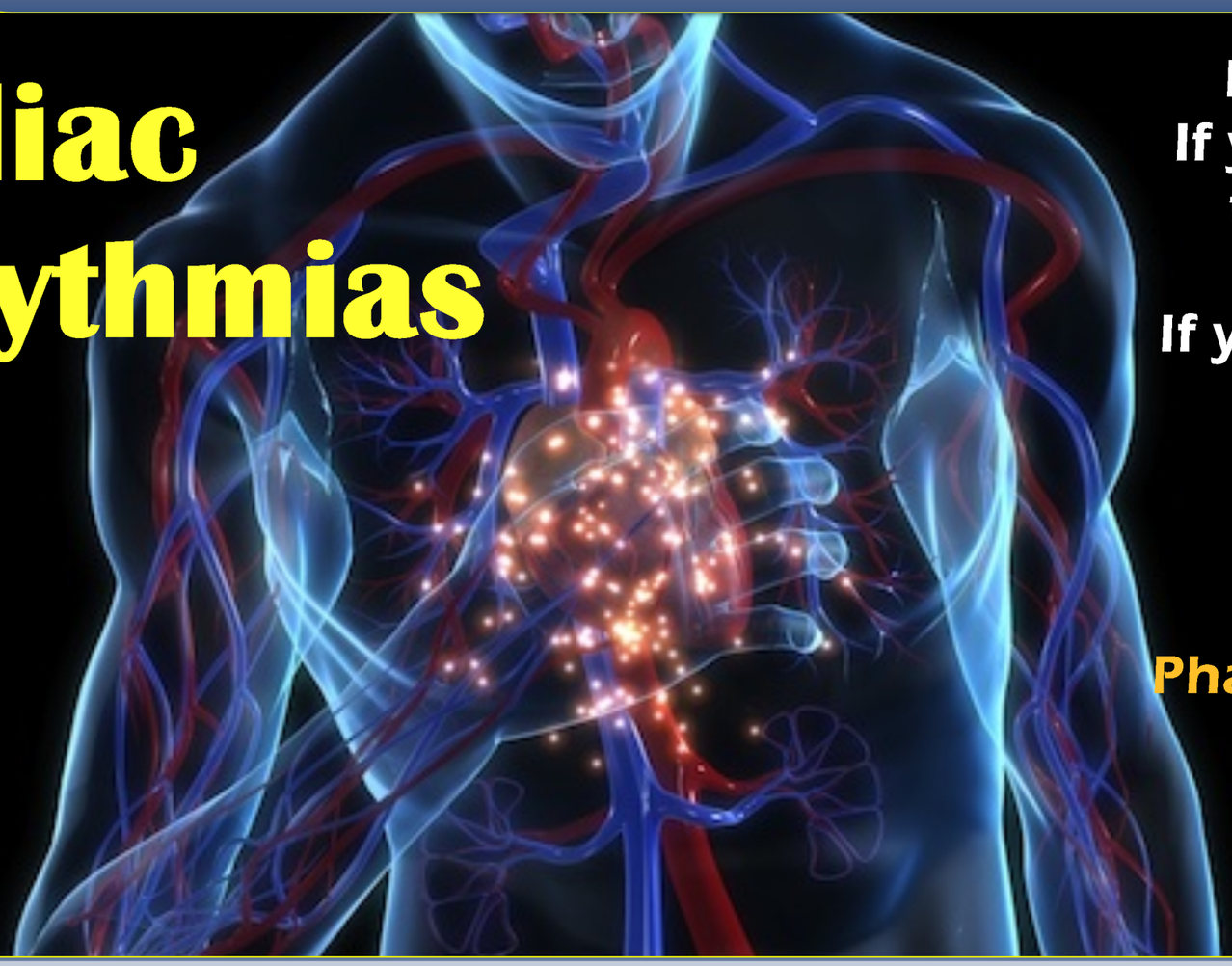
Draw Pharmacology *in your mind*



Cardiac arrhythmias



If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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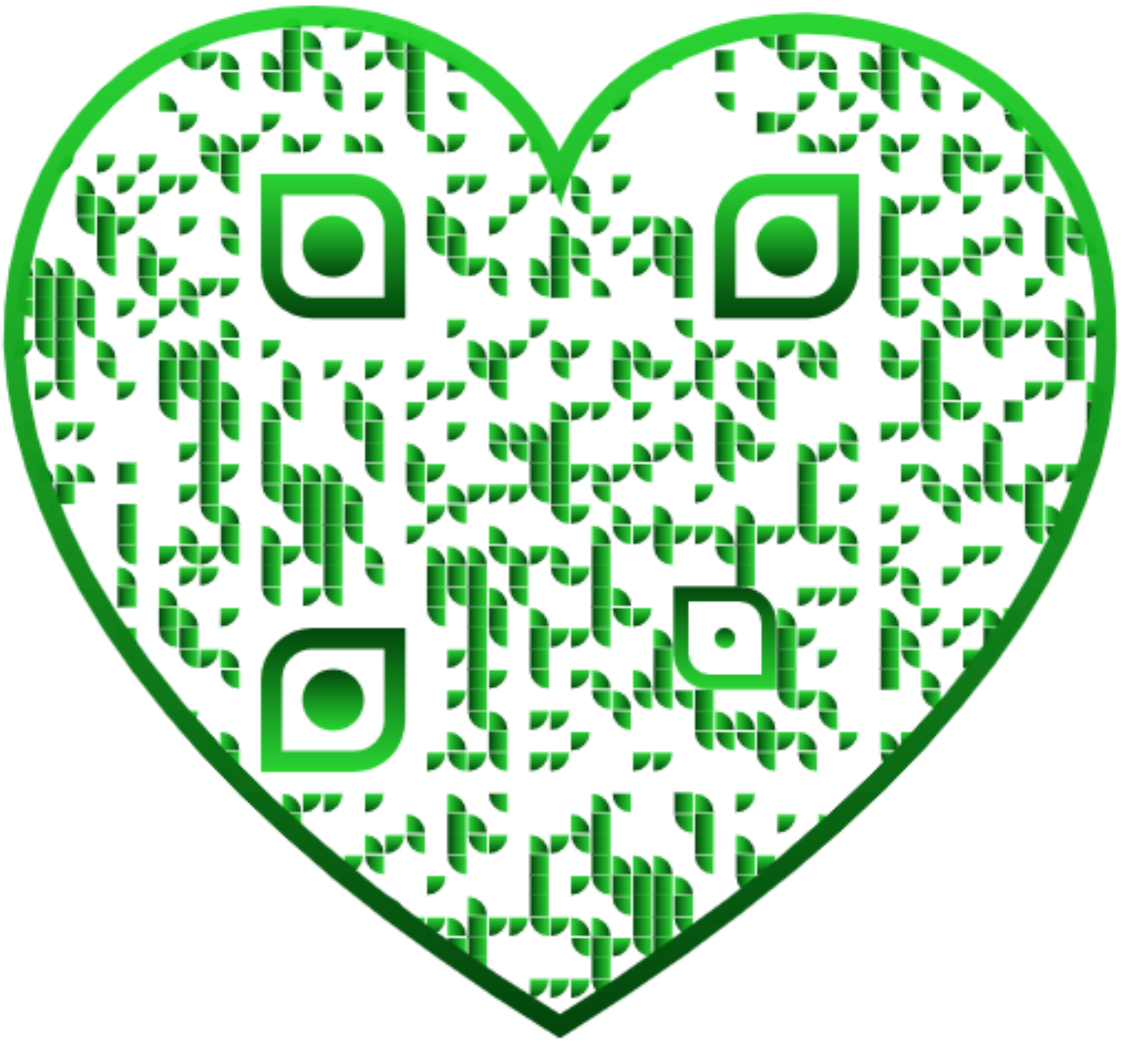
لا تنسونى من صالح دعائكم

Pharmacist. **Alaa Nasr** د. آلاء نصر



CARDIAC ARRHYTHMIAS

- **Arrhythmia is a disease characterized by:**
→ ⇑ in heart rate → **Tachyarrhythmia**
→ ⇓ in heart rate → **Bradyarrhythmia**

Types

1. Sinus arrhythmias

- It is **not pathological** → **Tachyarrhythmia**
- Common in **young healthy people**
- **Causes**
- Fever - Anemia - Excitement situations *(fight, fright, flight, happiness, sadness)* - Hyperthyroidism *(⇑levels of T_3 and T_4)* - Sympathomimetic drugs

2. Atrial flutter

- **It results from a diseased heart → Pathological** *(ex. Rheumatic fever - Myocarditis)*
- The atria beat very rapidly but **regularly** *(coordinated)*
- **Atrial rate = 300 beat/min**
- Not all these beats cause ventricular contraction **1/2** this number are delivered to ventricles
- **Ventricular rate = 150 beat/min**

Etiology

Ectopic focus → the heart will consider it as the new pacemaker *(it is a specific tissue in the heart that takes over the function of SAN because it has a **higher** beating rate than SAN, it beats regularly)*

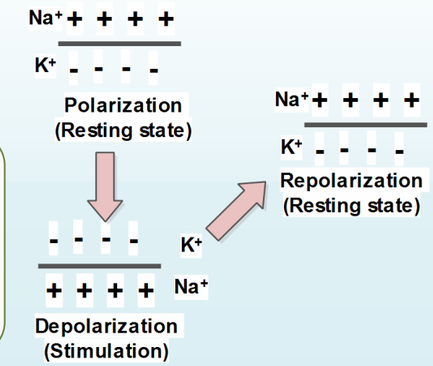
3. Atrial fibrillation

- **Atrial rate = 500 beat/min**
- **Ventricular rate = 80-100 beat/min**
- ONLY **1/5** of atrial beats are dilevered to ventricles ***WHY!!***
- As these 500 beats are not real, not strong beats but they are → *irrigular, very rapid, uncoordinated & fragmentary* → so, they can be called **muscle twitches**, palpitations, fibrillations → mechanically ineffective to pump blood → *most of them do not survive to reach AVN and AV bundle*
- As the artial rate is **not regular** → the ventricular systole will be **irrigular** and of variable strength

Atrial flutter is more dangerous than atrial fibrillation → as it may cause "ventricular fibrillation" → can lead to congestive heart failure (CHF)

Useful tips for understanding mechanisms .. Remember

- There is a **potential difference** across the plasma membrane of each cell where
→ *+ve charge accumulate outside the membrane*
→ *-ve charge accumulate inside the membrane*
- Any mechanical change in the muscle is preceded by electrical change *(electrical stimulus, depolarization)*



- In the heart the electrical change is initiated by an electrical stimulus from SAN or other electrical stimulus (Ectopic focus) → this electrical change is due to movement of ions → each type of ions has its specific type of channels:
→ **Na^+ channels** → blocked by tetradotoxin
→ **Ca^{+2} channels** → blocked by Nifidipine, Verapamil .. etc (calcium channel blockers CCBs)
- Ca^{+2} is present in the sarcoplasmic reticulum → it is released after depolarization to be free in the muscle fiber → helps in joining actin and myosin → leading to contraction
- The energy for muscle contraction is obtained from → hydrolysis of ATP by ATPase present in the muscle fibrils

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Antiarrhythmics

Mechanism

1. Class I

- They slow the depolarization process (⇑ refractory period) .. **How !**
- They cause **partial occlusion of Na^+ channels** → so, a higher concentration gradient should be established outside the membrane in order to cause excitation to the membrane
- So, rate of depolarization will ⇓ → and also outflux of Na^+ will be hindered → rate of repolarization will ⇓
- So, there will be **prolongation of depolarization-repolarization cycle**
- So, refractory period will ⇑ and speed of conduction will ⇓
→ Heart rate will be slowed down
- They are **membrane stabilizers** (have the ability to stabilize the membrane) = ⇓ its excitability = ⇑ threshold of excitation
- They are classified into **3 subclasses** according to their **affinity to Na^+ channels**

1) Class Ia

Quinidine

1. Cardiac actions

- **It has 2 actions that seem to be opposite !!**
1. **Depressant** effect on cardiac muscle
2. **Atropine-like** action (antivagal action, parasympatholytic)
- So, lets figure out are these 2 effects **parallel or opposite**

Effect on heart rate

In normal heart

- Here, **SAN** is the pacemaker of the heart → it is the least sensitive part in the heart to the depressant effect of Quinidine → **it receives vagal supply** *(inhibitory effect on the heart)*
- So, here Quinidine has both effects:
1. Depressant effect → little effect on SAN
2. Atropine-like action → inhibition on vagal action SAN → stimulation
→ **Opposite actions**
→ Net effect → ⇑ **heart rate**

In arrhythmic heart

- Here, the **Ectopic focus** is the pacemaker of the heart → it **does not receive vagal supply** *(not controlled by vagus nerve)*
- So, the depressant action of Quinidine predominates *(no antivagal action)* → ⇓ **heart rate**

Effect on refractory period

- Depressant action → ⇑ refractory period
- Atropine-like action → ⇑ refractory period *(vagal stimulation ⇓refractory period)*
→ So these are **parallel actions**

Effect on conduction velocity

- Depressant action → -----
- Atropine-like action → you should now that vagal stimulation ⇓ conductivity of the AV bundle → so, number of impulses transmitted from atria to ventricles ⇓
→ Quinidine has antivagal action → ⇑ conductivity of AV bundle → so, ⇓ atrial rate but ⇑ ventricular rate *(⇑velocity of conduction of AVN and AV bundle)* → so, may lead to **ventricular fibrillation**

2) Class Ib

Lidocaine

3) Class Ic

Flecainide

4) Class Id

Propafenone

2. Other actions

α-blocking action

- Cause vasodilatation → hypotension → leading to activation of compensatory mechanisms →
1. Reflex tachycardia !
2. Reflex stimulation of sympathetic nervous system !
→ Dangerous side effects → may **oppose** the main use !!

Effect on ECG

Prolongs PR interval, QRS complex, QT interval

Curare-like action

Neuromuscular blocking effect

→ So, regimen of **Digitalis** and **Quinidine** should be used for patients who have:
1. Recently developed atrial arrhythmia
2. Little or no impairment of ventricular arrhythmia
Why !
As digitalis ⇓the speed of conduction in AVN and AV bundle (Extravagal mechanism)
→ **Quinidine** for atria & **Digitalis** for ventricles

Antiarrhythmics

Ph. Alaa Nasr

1. Class I

1) Class Ia

Quinidine

1. Atrial flutter
2. Atrial fibrillation
3. Paroxysmal atrial tachycardia
4. Paroxysmal ventricular tachycardia

3. Uses

1. Administered orally as Quinidine sulphate
2. Rapidly absorbed - Hepatic metabolism - Excreted in urine (20% as it is)
3. Peak concentration in the plasma is attained in 60-90 min
4. 70-80% plasma protein binding → can be displaced by **Digitalis** → **TOXICITY**

4. Kinetics

5. Side effects & Toxicity

1. **GIT** → Nausea - Vomiting - Diarrhea
2. **CVS:**
- Severe depression → may cause heart failure in toxic doses
- Hypotension → due to α-blocking action
- Tachycardia → due to Atropine-like & α-blocking actions
- Complains of muscle weakness → due to curare-like action

Procainamide

- It has a pharmacological action similar to Procain *(a local anesthetic)* but it is **"amide"** so,
1. It is not readily metabolized by plasma esterase → ⇑ the duration of action
2. Effective orally
- Its cardiac actions are identical to those of Quinidine
- It can be administered **orally - IV - IM**

2) Class Ib

Phenytoin

- Anti-epileptic drug
- Large doses of it can abolish ventricular tachycardia

Lidocaine

- Local anesthetic
- Used in the treatment of ventricular arrhythmia

3) Class Ic

- It is the most recent antiarrhythmic drug class
- Firstly introduced in USA in 1986
- They are the most potent as they have high affinity to Na^+ channels
- **Examples: Flecainide - Encainide - Propafenone**

2. Class II

1. Example

β-blocker → **Propranolol** (Indral®)

2. Mechanism

- Sympatholytics → so, antagonizing the sympathetic effect on the heart
- Propranolol has a Quinidine-like action

3. Uses

Used as a **preanesthetic medication** before some general anesthetics such as **Halothane**
Notice that .. Halothane ⇑ the sensitivity of SAN to endogenous chatecholamines → ⇑ heart rate

4. Disadvantages

High doses can lead to **heart failure** → as they deprive the heart from sympathetic influence causing bradycardia then HF

Solution

1. Use β-blocker with ISA *(intrinsic sympathomimetic activity)* → partial agonist → **ex.Pindolol**
2. Coadministration with **Atropine** → ⇓ bradycardia *(blocks the inhibitory effect of parasympathetic nerve)*

May lead to **Asthma** → due to non-selectivity → it may block β_2 receptors in lungs → bronchoconstriction

Solution

Use a selective β_1 blocker → **ex. Atenolol**

3. Class III

They prolong the refractory period of cardiac muscle by other mechanisms
ex. Amiodarone (Cordarone®)

4. Class IV

They are Ca^{+2} channel blockers → interfering with the entry of Ca^{+2} → so, ⇓ force of contraction
ex.
Verapamil (Cardiomil® - Isoptin®)
Deltiazem (Delay-tiazem® - Altiazem®)
Cinnarazine (Stugeron® - Cinibral®)
Nifedipine (Epilat® - Adalat®)
Nicardipine (Pelcard®)